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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/876,997	06/08/2001	Jean-Baptiste Dumas Milne Edwards	78.US4.CIP	2239

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SALIWANCHIK LLOYD & SALIWANCHIK
A PROFESSIONAL ASSOCIATION
2421 N.W. 41ST STREET
SUITE A-1
GAINESVILLE, FL 326066669

EXAMINER	
RAMIREZ, DELIA M	
ART UNIT	**PAPER NUMBER**
1652	13

DATE MAILED: 08/21/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/876,997	DUMAS MILNE EDWARDS ET AL.	
	Examiner	Art Unit	
	Delia M. Ramirez	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 May 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *23-34* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *23-34* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☒ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *7,10* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: *alignments* .

DETAILED ACTION

Status of the Application

Claims 22-34 are pending.

Applicant's election without traverse of Group IV (claims 13-15 drawn to a polypeptide) and the amino acid sequence of SEQ ID NO: 399, in Paper No. 12, filed on 5/22/2003 is acknowledged.

Applicant's amendment canceling claims 1-22 and adding claims 23-34, in Paper No. 12, filed on 5/22/2003 is acknowledged. Newly added claims 23-34 will be examined since they are all directed to the elected subject matter, i.e. the polypeptide of SEQ ID NO: 399.

Priority

1. Acknowledgment is made of a claim for domestic priority under 35 U.S.C. 119(e) to provisional application No. 60/169,629 filed on 12/08/1999, and 60/187,470 filed on 03/06/2000.

2. Acknowledgment is made of a claim for domestic priority under 35 U.S.C. 120 or 121 to US application No. 09/731,872 filed on 12/07/2000.

3. It is noted that SEQ ID NO: 399 was first disclosed in U.S. Application No. 60/169,629, filed on 12/08/1999.

Information Disclosure Statement

4. The information disclosure statements (IDS) submitted on 2/11/2002 and 1/21/2003 are acknowledged. The reference listed in the information disclosure statement filed on 2/11/2002 as "O" is not in conformance with MPEP § 609 and has not been considered for the following reasons. There is no publication date and no indication as to where was this reference first published. It appears that such reference is an Abstract from a scientific conference. It is suggested that the name of the organization and the conference as well as the date when it took place be added. The remaining references in the

submissions are in compliance with the provisions of 37 CFR 1.97 and are being considered by the Examiner.

Drawings

5. The drawings have been reviewed and are objected under 37 CFR 1.84 or 1.152. See attached Notice of Draftsperson's Patent Drawing Review. Applicant is required to submit the drawing corrections within the time period set in the attached Office communication. See 37 CFR 1.85(a). Failure to take corrective action within the set period will result in ABANDOMENT of the application. In addition, if amendments to the specification are needed due to drawing corrections, Applicant is requested to submit such amendments while the case is being prosecuted to expedite the processing of the application.

Claim Objections

6. Claims 23-24 are objected to because of the following informalities: the term "an amino acid sequence of SEQ ID NO: 399" should be "the amino acid sequence of SEQ ID NO: 399" since such sequence is defined by its sequence identifier. Appropriate correction is required.

Claim Rejections - 35 USC § 112, Second Paragraph

7. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

8. Claims 33-34 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

9. Claims 33-34 are indefinite in the recitation of "the polypeptide of claim 29 comprising (consisting of) the amino acid sequence of SEQ ID NO: 399" for the following reasons. Claims 33-34

depend from claim 26. As such, claims 33-34 are directed to an allelic variant of a polypeptide comprising the polypeptide the amino acid sequence of SEQ ID NO: 399, wherein said allelic variant comprises (consists of) the amino acid sequence of SEQ ID NO: 399. Therefore, it is unclear as to how claims 33-34 are any different from claims 23-24. For examination purposes, claims 33-34 will be considered duplicates of claims 23-24. Correction is required.

Claim Rejections - 35 USC § 101

10. 35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

11. Claims 23-34 are rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a substantial and specific asserted utility or a well established utility.

Claims 23-34 are directed to the polypeptide of SEQ ID NO: 399 and allelic variants thereof. The specification discloses that the polypeptide of SEQ ID NO: 399 is homologous to proteins of the phosphatidic acid phosphatase type 2 (PAP2) superfamily and that it has a pfam characteristic domain of the PAP2 superfamily from positions 19 to 175. Therefore, based on structural homology, the specification asserts that the polypeptide of SEQ ID NO: 399 is a phosphatidic acid phosphatase and is referred to as PAP7 (page 321, lines 3-15). While Applicants have proposed a function for the polypeptide of SEQ ID NO: 399, and have propose a variety of uses for this protein, the instant polypeptide does not meet the utility requirements for the following reasons.

The asserted function for the polypeptide of SEQ ID NO: 399 is based solely upon structural homology and the specification does not provide any empirical evidence that the polypeptide of SEQ ID NO: 399 is a phosphatidic acid phosphatase (PAP). The state of the art suggest that structural homology (i.e. sequence identity) alone is insufficient to accurately predict a polypeptide's function, and that

sequence homology alone should not be used to determine a protein's function. Bork (Genome Research, 10:348-400, 2000) teaches that protein function is context dependent, and both molecular and cellular aspects must be considered (page 398). Attwood (Science, 290(5491):471-473, 2000; pages 1-5 in HTML copy supplied to Applicants) teaches that structure prediction methods are unreliable and that it is presumptuous to make functional assignments merely on the basis of some degree of similarity between sequences (page 1 of HTML copy, second paragraph). Furthermore, Attwood teaches that using structural similarity to domains (i.e. modules) to assign function is unpredictable since proteins are complex systems comprising several domains (i.e. folding units, modules) that together can confer a variety of functions on a protein, therefore if the best hit in a database search is a match to a single domain, the function associated with such hit may not reflect the actual function of the protein of interest (page 3, lines 21-31 of HTML copy).

The art also shows several examples of variants with high degree of similarity with different function. Witkowski et al. (Biochemistry 38:11643-11650, 1999) teaches that one amino acid substitution transforms a β-ketoacyl synthase into a malonyl decarboxylase and completely eliminates β-ketoacyl synthase activity. Van de Loo et al. (Proc. Natl. Acad. Sci. 92:6743-6747, 1995) teaches that polypeptides of approximately 67% homology to a desaturase from *Arabidopsis* where found to be hydroxylases once tested for activity. Seffernick et al. (J. Bacteriol. 183(8):2405-2410, 2001) teaches that two naturally occurring Pseudomonas enzymes having 98% amino acid sequence identity catalyze two different reactions: deamination and dehalogenation, therefore having different function. Broun et al. (Science 282:1315-1317, 1998) teaches that as few as four amino acid substitutions can convert an oleate 12-desaturase into a hydrolase and as few as six amino acid substitutions can transform a hydrolase to a desaturase.

In the instant case, an alignment of the polypeptide of SEQ ID NO: 399 against human PAP proteins shows that the polypeptide of SEQ ID NO: 399 is at best 18.4% , 17.9% and 17.8% sequence

homologous with human phosphatidic acid phosphatase type-2C, 2B, and 2A, respectively. See attached alignments. In regard to Applicant's assertion that there is a pfam characteristic domain of the PAP2 superfamily present in the polypeptide of SEQ ID NO: 399 from positions 19 to 175, it is noted that an alignment of this fragment against human PAP proteins shows an extremely low sequence homology in that region. Amino acids 19-175 of SEQ ID NO: 399 are at best 21.4%, 20.8%, and 20.6% sequence homologous to human phosphatidic acid phosphatase type 2C, 2B, and 2A, respectively. See attached alignments. Therefore, in view of the extremely low sequence homology between the polypeptide of SEQ ID NO: 399 and human PAPs, as well as the low sequence homology between amino acids 19-175 of SEQ ID NO: 399 and human PAPs, the teachings of the art in regard to assigning function based on structural homology, and the lack of experimental evidence corroborating Applicant's assertion in regard to function, one cannot reasonably conclude that the asserted utility is a well established utility for the claimed polypeptides. Furthermore, Applicant's asserted utility constitute a utility that requires further research to identify or reasonably confirm a "real world" context of use. See e.g., Brenner v. Manson, 383 U.S. 519, 148 USPQ 689 (Sup. Ct. 1966). This type of utility is not considered a "substantial utility". An assay that detects the presence of an agent that has a stated correlation to a predisposition to the onset of a specific disease condition would be considered a "substantial utility" in the context of identifying potential candidates for preventive measures. Here the instant polypeptide is suitable only for additional research. Thus, applicants have not disclosed a well established and substantial utility for the claimed polypeptide, and allelic variants thereof.

12. Claims 23-34 are also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

13. **In case Applicant overcomes this utility rejection by providing convincing evidence in response to this Office Action, the following rejections will apply:**

Claim Rejections - 35 USC § 112, First Paragraph

14. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

15. Claims 26, 29, and 32 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claim 26 is directed to a genus of allelic variants of the polypeptide of SEQ ID NO: 399. Claims 29 and 32 are directed to the genus of allelic variants of claim 26 wherein said allelic variants are phosphatases, including those catalyzing the conversion of phosphatidic acid into diacylglycerol. While the specification discloses the structure of the polypeptide of SEQ ID NO: 399 and states that the instant polypeptide is homologous to proteins of the phosphatidic acid phosphatase type 2 superfamily (PAP2; page 321, lines 3-5), the specification is silent in regard to the structure of allelic variants of the polypeptide of SEQ ID NO: 399 which have phosphatase activity or the potentially different functions allelic variants of the polypeptide of SEQ ID NO: 399 may have.

The specification defines an allelic variant as one of several alternate forms of a gene occupying a given locus on a chromosome of an organism (page 36, lines 30-32). Therefore, alleles may result in altered mRNAs or polypeptides whose structure or function may or may not be altered. This definition does not provide any specific information about the structure of allelic variants (i.e. alleles) of the gene

which encodes the polypeptide of SEQ ID NO: 399 (i.e. where are the regions within which structural changes are likely to occur) nor discloses any function for allelic variants. There is no description of the mutational sites that exist in nature, and there is no description of how the structure of the cDNA encoding the polypeptide of SEQ ID NO:399 relates to the structure of any naturally occurring allele. The general knowledge in the art concerning alleles does not provide any indication of how one allele is representative of unknown alleles. There is no indication in the art that would suggest that the structure of one provides guidance to the structure of others. In addition, the disclosure fails to provide any information as to the critical structural elements a polynucleotide should have to encode a polypeptide with phosphatase activity or able to catalyze the conversion of phosphatidic acid into diacylglycerol. The specification discloses only a single species of the claimed genus (i.e. the polypeptide of SEQ ID NO:399 and its corresponding cDNA SEQ ID NO: 158) which is insufficient to put one of skill in the art in possession of the attributes and features of all species within the claimed genus. Therefore, one skilled in the art cannot reasonably conclude that the applicant had possession of the claimed invention at the time the instant application was filed. Applicant is referred to the revised interim guidelines concerning compliance with the written description requirement of U.S.C. 112, first paragraph, published in the Official Gazette and also available at the USPTO website.

16. Claims 25, 28, and 31 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The instant invention requires clone 160-40-1-0-H4-CS. Since this clone is essential to the claimed invention, it must be obtainable by a repeatable method set forth in the specification or otherwise be readily available to the public. The instant clone is not fully disclosed, nor have all the sequences

required for its construction been shown to be publicly known and freely available. The enablement requirements of 35 U.S.C. § 112 may be satisfied by a deposit of the instant clone. The specification does not disclose a repeatable process to obtain the clone and it is not apparent if the DNA sequences are readily available to the public. Accordingly, it is deemed that a deposit of this clone should have been made in accordance with 37 CFR 1.801-1.809.

It is noted that applicants have deposited several different clones, including clone 160-40-1-0-H4-CS, under ATCC accession number PTA-1218. However, there is no indication in the specification as to public availability. If the deposit was made under the terms of the Budapest Treaty, then an affidavit or declaration by applicants, or a statement by an attorney of record over his or her signature and registration number, stating that the clone has been deposited under the Budapest Treaty and that it will be irrevocably and without restriction or condition released to the public upon the issuance of the patent, would satisfy the deposit requirement made herein.

If the deposit has not been made under the Budapest treaty, then in order to certify that the deposit meets the criteria set forth in 37 CFR 1.801-1.809, applicants may provide assurance or compliance by an affidavit or declaration, or by a statement by an attorney of record over his or her signature and registration number, showing that:

a. during the pendency of this application , access to the invention will be afforded to the Commissioner upon request;

b. all restrictions upon availability to the public will be irrevocably removed upon granting of the patent;

c. the deposit will be maintained in a public repository for a period of 30 years or 5 years after the last request or for the effective life of the patent, whichever is longer; and

d. the deposit will be replaced if it should ever become non-viable.

17. Even if the utility rejection applied above is overcome, the following rejection would apply. Claims 26, 29, and 32 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the polypeptide of SEQ ID NO: 399, does not reasonably provide enablement for any allelic variant of the polypeptide of SEQ ID NO: 399. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The criteria for undue experimentation, summarized in *re Wands*, 8, USPQ2nd 1400 (Fed. Cir. 1988) are: 1) quantity of experimentation necessary, 2) the amount of direction or guidance presented, 3) the presence and absence of working examples, 4) the nature of the invention, 5) the state of prior art, 6) the relative skill of those in the art, 7) the predictability or unpredictability of the art, and 8) the breath of the claims.

The scope of the claim, as described above, is not commensurate with the enablement provided in regard to the large number of allelic variants of different functions which have not been described and for which there is no specific use or structure disclosed, as encompassed by the claims. The specification discloses the structure of the polypeptide of SEQ ID NO: 399 and indicates that the instant polypeptide is structurally homologous to PAP2 proteins, but there is no disclosure of the function and structure of other allelic variants as encompassed by the claims, nor there is disclosure of the critical structural elements required in a polypeptide to be an allelic variant of the polypeptide of SEQ ID NO: 399 and display the recited function..

As indicated above, the genus of polypeptides encompassed by the claims can potentially include proteins of diverse function. While one could argue that one of skill in the art would know how to use a human phosphatase which converts phosphatidic acid into diacylglycerol, the specification fails to provide any guidance as to how one of skill in the art can (1) determine other functions for the claimed polypeptides, (2) use the polypeptides of (2) without undue experimentation, and (3) construct the

claimed polypeptides in the absence of some guidance or knowledge as to how structure correlates with function. The state of the art clearly teaches the unpredictability of determining function of structural homologs based on sequence homology and how small structural changes lead to major changes in function. See the teachings of Bork, Broun et al., Van de Loo et al., Seffernick et al., and Witkowski et al. (Biochemistry 38:11643-11650, 1999) already discussed above. Therefore, due to the lack of relevant examples, the amount of information provided, and the unpredictability of the prior art in regard to function based on structural homology, one of ordinary skill in the art would have to go through the burden of undue experimentation in order to (1) determine the function of those polypeptides as encompassed by the claims, (2) how to use the polypeptides of (1), and (3) how to construct allelic variants of the polypeptide of SEQ ID NO: 399 having phosphatase activity in the absence of any teaching as to how structure correlates with function. Thus, Applicant has not provided sufficient guidance to enable one of ordinary skill in the art to make and use the invention in a manner reasonably correlated with the scope of the claims.

Double Patenting

18. It is noted that the application Serial No. 09/731,872 discloses a polypeptide identical to that of SEQ ID NO: 399 of the instant application. Since application Serial No. 09/731,872 is not available to the examiner at this time, no determination has been made as to whether or not a double patenting rejection should be applied to the claims of the instant application. If, upon availability of the above application to the examiner, it is determined that there are conflicting claims between application Serial No. 09/731,872 and the instant application, double patenting will not be considered as new ground(s) of rejection.

Conclusion

19. No claim is in condition for allowance.

20. Applicants are requested to submit a clean copy of the pending claims (including amendments, if any) in future written communications to aid in the examination of this application.

21. Certain papers related to this application may be submitted to Art Unit 1652 by facsimile transmission. The FAX number is (703) 308-4556. The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 CFR 1.6(d)). NOTE: If Applicant submits a paper by FAX, the original copy should be retained by Applicant or Applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED, so as to avoid the processing of duplicate papers in the Office.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Delia M. Ramirez whose telephone number is (703) 306-0288. The examiner can normally be reached on Monday-Friday from 8:30 AM to 5:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. Ponnathapura Achutamurthy can be reached on (703) 308-3804. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Delia M. Ramirez, Ph.D.
Patent Examiner
Art Unit 1652

DR
August 19, 2003

REBECCA E. PROUTY
PRIMARY EXAMINER
GROUP ~~1300~~ 1600